[Official Title]

|  |  |
| --- | --- |
| Short title | [Fill in] |
| Acronym / Protocol code | [Acronym / Protocol code] |
| Protocol version numberProtocol version date | [Protocol version number][Protocol version date] |
| EU reference number | [EU reference number] |
| Phase of the trial | [Choose phase from the list] |
| Sponsor | [Choose Sponsor from the list][Choose Address from the list]Belgium |
| Financial/Material support | [Fill in] |
| Coordinating Investigator | [Name CI][Contact details CI] |

[Official Title]

Protocol Coordinating Investigator signature page

I certify that I will conduct the trial in compliance with the protocol, any modifications, GCP and the declaration of Helsinki, the CTR and all other applicable regulatory requirements.

**Investigator:**

|  |  |
| --- | --- |
| Name: | [Fill in] |
| Function: | [Fill in] |
| Institution: | [Fill in] |

|  |  |
| --- | --- |
| **Date:** | [Choose date] |
| **Signature:** |  |

[Official Title]

Protocol Site Principal Investigator signature page

I certify that I will conduct the trial in compliance with the protocol, any modifications, GCP and the declaration of Helsinki, the CTR and all other applicable regulatory requirements.

|  |  |
| --- | --- |
| Name: |  |
| Function: |  |
| Institution: |  |

|  |  |
| --- | --- |
| **Date:** |  |
| **Signature:** |  |

# Protocol modification history

|  |  |  |
| --- | --- | --- |
| **Version** | **Date** | **Description of modification** |
| 1.0 | [Choose date] | Initial submission to CA/IEC. |
| [Fill in] | [Choose date] | [Fill in] |

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# Protocol synopsis

## Protocol synopsis in English

|  |  |
| --- | --- |
| **Title** | [Official Title] |
| **Acronym / Protocol code** | [Acronym / Protocol code] |
| **Protocol version number** | [Protocol version number] |
| **Protocol version date** | [Protocol version date] |
| **EU reference number** | [EU reference number] |
| **Sponsor** | [Choose Sponsor from the list][Choose Address from the list]Belgium |
| **Coordinating Investigator** | [Fill in] |
| **Rationale** | [Fill in] |
| **Objective** | [Fill in] |
| **Main trial endpoints** | [Fill in] |
| **Secondary trial endpoints** | [Fill in] |
| **Trial population** | [Fill in] |
| **Number of participants** | [Total number of subjects] |
| **Trial design** | [Fill in] |
| **Total trial duration** | [Fill in] |
| **Interventions** | [Fill in] |
| **Ethical considerations** | [Fill in] |

## Protocol synopsis in the language of the subjects (Dutch)

|  |  |
| --- | --- |
| **Officiële titel** | [Official Title] |
| **Nederlandstalige vertaling van de titel van de proef** | [Fill in] |
| **Acroniem / Protocolcode** | [Acronym / Protocol code] |
| **Protocolversie nummer** | [Protocolversie nummer ] |
| **Protocolversie datum** | [Protocolversie datum] |
| **EU-nummer van de proef** | [EU reference number] |
| **Opdrachtgever** | [Choose Sponsor from the list][Choose Address from the list]Belgium |
| **Coordinating Investigator** | [Fill in] |
| **Motivering** | [Fill in] |
| **Doelstelling** | [Fill in] |
| **Belangrijkste eindpunten** | [Fill in] |
| **Secundaire eindpunten** | [Fill in] |
| **Studiepopulatie** | [Fill in] |
| **Aantal deelnemers** | [Total number of subjects] |
| **Opzet van de proef** | [Fill in] |
| **Totale duurtijd van de proef** | [Fill in] |
| **Interventies** | [Fill in] |
| **Ethische overwegingen** | [Fill in] |

## Protocol synopsis in the language of the subjects (French)

|  |  |
| --- | --- |
| **Titre officiel** | [Official Title] |
| **Traduction française du titre de l’essai clinique** | [Fill in] |
| **Acronyme / Code de protocole** | [Acronym / Protocol code] |
| **Numéro de version du protocole** | [Numéro de version du protocole] |
| **Date de version du protocole** | [Date de version du protocole] |
| **Numéro UE d’essai** | [EU reference number] |
| **Promoteur** | [Choose Sponsor from the list][Choose Address from the list]Belgium |
| **Coordinating Investigator** | [Fill in] |
| **Justification de la recherche**  | [Fill in] |
| **Objectif** | [Fill in] |
| **Critères de jugement primaires** | [Fill in] |
| **Critères de jugement secondaires** | [Fill in] |
| **Population des participants** | [Fill in] |
| **Nombre de participants** | [Total number of subjects] |
| **Déroulement de l’essai** | [Fill in] |
| **Durée total de l’essai** | [Fill in] |
| **Interventions** | [Fill in] |
| **Enjeux éthiques** | [Fill in] |

## Protocol synopsis in the language of the subjects (German)

|  |  |
| --- | --- |
| **Offizieller Titel** | [Official Title] |
| **Deutsche Titelübersetzung der klinischen Prüfung** | [Fill in] |
| **Akronym / Prüfplan Nummer** | [Acronym / Protocol code] |
| **Prüfplan Versionsnummer** | [Prüfplan Versionsnummer] |
| **Prüfplan Versionsdatum** | [Prüfplan Versionsdatum] |
| **EU-Prüfungsnummer** | [EU reference number] |
| **Sponsor** | [Choose Sponsor from the list][Choose Address from the list]Belgium |
| **Coordinating Investigator** | [Fill in] |
| **Motiv für die Prüfung** | [Fill in] |
| **Zielsetzung** | [Fill in] |
| **Primäre Endpunkte** | [Fill in] |
| **Sekundäre Endpunkte** | [Fill in] |
| **Gruppe der Prüfungsteilnehmer** | [Fill in] |
| **Zahl der Teilnehmer** | [Total number of subjects] |
| **Prüfungsaufbau** | [Fill in] |
| **Gesamtdauer der Prüfung** | [Fill in] |
| **Interventionen** | [Fill in] |
| **Ethische Erwägungen** | [Fill in] |

# Introduction

## Rationale

[Fill in]

## Background

[Fill in]

## Risk/Benefit assessment

[Fill in]

A separate trial-specific risk assessment plan (RAP) will be available to address, in detail, the most relevant potential risks and to specify the mitigation of those risks. Risks will be scaled into low, medium and high risks.

## Patient participation in trial design

[Fill in]

# Objectives

## Main objectives

[Fill in]

## Secondary objectives

[Fill in]

## Exploratory objectives

[Fill in]

# End points

## Primary end points

[Fill in]

## Secondary end points

[Fill in]

## Exploratory end points

[Fill in]

# Trial design

## Overall design

### Design description

[Fill in]

### Design rationale

[Fill in]

### Flowchart

[Fill in]

## Start of the trial

The trial is considered started upon the first act of recruitment of a potential subject. For this trial this is considered as [Fill in].

The start of the trial shall be notified to the CA/IEC within 15 calendar days.

The first visit of the first subject (i.e. when the first subject or his/her legally designated representative signs his/her first informed consent to participate in the trial) (FVFS) will also be notified to the CA/IEC within 15 calendar days.

## End of the trial

### For an individual subject

The subject has completed the trial when [Choose from the list or fill in].

### For the whole trial

The end of the recruitment of subjects shall be notified to the CA/IEC within 15 calendar days.

Overall, the end of the trial is reached when [Choose from the list or fill in].

As soon as the whole trial has ended (cfr. the definition above), the CA/IEC shall be notified within 15 calendar days.

A summary of the results of the trial will be submitted to the CA/IEC within 1 year from the end of the trial, irrespective of the outcome of the trial.

## Trial duration

### For an individual subject

[Fill in]

### For the whole trial

[Fill in]

# Trial population

## Number of subjects and planned recruitment rate

[Total number of subjects] subjects will be included in this trial.

It is expected that overall an accrual rate of [Fill in] subjects per [Choose from the list] is realistic in the whole trial.

## Inclusion and exclusion criteria

### Inclusion criteria

[Fill in]

### Exclusion criteria

[Fill in]

### Justification of in- and exclusion criteria

[Fill in]

## Withdrawal and replacement of subjects

### Withdrawal of subjects

Subjects are free to withdraw from participation in the trial at any time. A subject must be discontinued from the trial if [Choose from the list] withdraws consent.

An investigator may withdraw a subject from the trial for the following reasons:

* Pregnancy;
* Significant trial intervention non-compliance;
* If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the trial would not be in the best interest of the subject;
* Disease progression which requires discontinuation of the trial intervention;
* If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further trial participation;
* Subject unable to receive [Fill in] for [Fill in] [Choose from the list];
* [Fill in]

In all cases, the reason why subjects are withdrawn must be recorded in detail in the electronic Case Report Form (eCRF) and in the subject’s medical records. The gathered subject data should be taken into account in the analysis of the trial data.

A subject will be considered lost to follow-up if he or she fails to return for [Fill in] scheduled visits and is unable to be contacted by the trial site staff.

The following actions must be taken if a subject fails to return for a required trial visit:

* The site will attempt to contact the subject and reschedule the missed visit within [Fill in] and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the trial;
* Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (i.e. three telephone calls and a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s medical record or study file;
* Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.
* [Fill in]

### Replacement of subjects

[Fill in]

### Follow-up of withdrawn subjects

Regardless of the reason for withdrawal, the Principal Investigator (PI) must consider the following:

* Procedures for safe discontinuation of participation;
* Retention and use of the data already collected.

[Fill in]

## Method of recruitment and compensation for subjects

[Fill in]

## Subject eligibility screening

Screen failures are subjects who consent to participate in the trial but do not meet one or more criteria required for participation in the trial during the screening procedures. Screen failures will not be enrolled in the trial. A minimal set of screen failure information will be kept to ensure transparent reporting of screen failure subjects.

Screen failures [Choose from the list].

## Subject follow-up after trial participation

[Fill in]

# Investigational Medicinal Product (IMP)

## <Name of the IMP>

### General information

|  |  |
| --- | --- |
| Also refer to | [Choose from list] |
| Name of the IMP | [Fill in] |
| Qualitative and quantitative composition | [Fill in] |
| Pharmaceutical form | [Fill in] |
| Method of administration | [Fill in] |
| Authorised in the EU | [Choose from list] |
| Used within scope | [Choose from list] |
| Marketing authorisation holder | [Fill in] |
| Marketing authorisation number(s) | [Fill in] |
| Manufacturer | [Fill in] |
| Distributor | [Fill in] |
| Responsible for batch release | [Fill in] |

### IMP rationale

[Fill in]

### Preparation of the IMP

[Fill in]

### Administration, dosage and dose frequency of the IMP

[Fill in]

### Permitted dose adjustments and interruption of treatment

[Fill in]

### Duration of treatment

[Fill in]

### Packaging and labeling of the IMP

[Fill in]

### Traceability, storage, return and destruction of the IMP

[Fill in]

# Auxiliary Medicinal Product (AxMP)

## <Name of the AxMP>

### General information

|  |  |
| --- | --- |
| Also refer to | [Choose from list] |
| Name of the AxMP | [Fill in] |
| Qualitative and quantitative composition | [Fill in] |
| Pharmaceutical form | [Fill in] |
| Method of administration | [Fill in] |
| Authorised in the EU | [Choose from list] |
| Used within scope | [Choose from list] |
| Marketing authorisation holder | [Fill in] |
| Marketing authorisation number(s) | [Fill in] |
| Manufacturer | [Fill in] |
| Distributor | [Fill in] |
| Responsible for batch release | [Fill in] |

### AxMP rationale

[Fill in]

### Preparation of the AxMP

[Fill in]

### Administration, dosage and dose frequency of the AxMP

[Fill in]

### Permitted dose adjustments and interruption of treatment

[Fill in]

### Duration of treatment

[Fill in]

### Packaging and labeling of the AxMP

[Fill in]

### Traceability, storage, return and destruction of the AxMP

[Fill in]

# Concomitant medication and treatment

### Concomitant medication

[Fill in]

### Concomitant treatment

[Fill in]

# Study specific procedures

## Eligibility screening process

[Fill in]

Also refer to section 6.5.

## Informed consent

Refer to section 16.2.

## Measures taken to minimise bias

### Randomisation

[Fill in]

### Blinding

[Fill in]

### Deblinding procedures

The study code should only be broken for valid medical or safety reasons, e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the subject is receiving before he or she can be treated. If possible, other study team members should remain blinded.

The code breaks for the trial are kept at [Fill in]; in the event a code is required to be unblinded a formal request for unblinding will be made by the local PI to the Coordinating Investigator (CI).

The CI/PI documents the breaking of the code and the reasons for doing so on the eCRF/study documents, in the site file and medical notes. It will also be documented at the end of the trial in any final study report and/or statistical report.

The study team will notify the Sponsor in writing as soon as possible following the code break detailing the necessity of the code break.

As the investigator is responsible for the medical care of the individual study subject (Declaration of Helsinki §3 and ICH 4.3) the coding system should include a mechanism that permits rapid unblinding (ICH GCP 5.13.4). The investigator cannot be required to discuss unblinding if he or she feels that emergent unblinding is necessary.

### Other measures taken to minimise bias

[Fill in]

## Study specific interventions

[Fill in]

Since the subjects are not under 24-hour supervision of the investigator or his/her staff, they will be provided with a study card indicating at least the name of the investigational medicinal product, the dosage, the PI’s name and a 24-hour emergency contact number.

## Restrictions for subjects during the trial

[Fill in]

## Overview of collected data

[Fill in]

## Schematic overview of the data collection and interventions

*Example of a table:*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | ***Screening visit******(T-1)*** | ***Visit 1 / Baseline******(T0)*** | ***Visit 2 (1 month)******(T1)*** | ***Visit 3 (2 months)******(T2)*** | ***Follow-up visit (6 months) (T3)*** |
| ***Informed consent*** | *X* |  |  |  |  |
| ***Inclusion/exclusion criteria check*** | *X* |  |  |  |  |
| ***Pregnancy test (urine stick)*** | *X* | *X* | *X* | *X* | *X* |
| ***Randomisation*** | *X (between T-1 and T0)* |  |  |  |
| ***Study specific intervention A*** |  |  | *X* | *X* |  |
| ***Study specific intervention B*** |  |  | *X* | *X* |  |
| ***Blood analysis******(6 ml blood)*** | *X\** | *X* | *X* | *X* | *X\** |
| ***Study specific intervention D*** |  |  | *X* | *X* |  |
| ***Drug intake*** |  | *X (from T0 until T2, every day 3x 5mg)* |  |
| ***Questionnaire XYZ*** | *X (from T-1 until T3, once every week)* |
| ***Drug accountability*** |  |  | *X* | *X* |  |
| ***Adverse event check*** |  |  | *X* | *X* | *X* |

*\* Intervention is standard of care and is being performed regardless of inclusion in the trial.*

# Biological samples

## Types and number of samples

[Fill in]

## Timepoints of sample collection

[Fill in]

## Sample handling and analysis

[Fill in]

## Sample storage and shipment

[Fill in]

## Future use of stored samples

[Fill in]

# Statistical considerations

## Sample size calculation, power calculation, significance level

The [Choose from list] on which the sample size calculation is based upon, [Choose from list] [Fill in].

The calculation of the sample size used the tool [Fill in] and included the following parameters: [Fill in].

[Fill in]

## Type of statistical methods

[Fill in]

## Statistical analysis team

[Fill in]

## Interim analysis

[Fill in]

# Data handling

## Method of data collection

An electronic data capture (EDC) system, i.e. REDCap, will be used for data collection. REDCap is provided and maintained by Vanderbilt University; a license for use was granted to the Health, Innovation and Research Institute (HIRUZ). REDCap is a web-based system.

### Case Report Form (CRF)

Only the data required by the protocol are captured in the eCRF. The eCRFs and the database will be developed, based on the protocol. The final eCRF design will be approved by the CI.

The study site staff is responsible for data entry in REDCap.

Subjects that are included in the trial, will be assigned a unique study number upon their registration in REDCap. On all documents submitted to the sponsor or CI, subjects will [Choose from list]. REDCap has built-in options for univariate alerts, such as valid-value, valid-range, and missing-value alerts.

Data reported on each eCRF should be consistent with the source data. If information is not known, this must be clearly indicated on the eCRF. All missing and ambiguous data will be clarified.

All data entries and corrections will only be performed by study site staff, authorised by the Investigator. Data will be reviewed by trained personnel (monitor, data manager) and any errors or inconsistencies will be clarified.

### Data directly collected in the CRF (no source available)

[Fill in]

## Data storage

The data is accessed through a web browser directly on the secure REDCap server. The server is hosted within the Ghent University Hospital campus and meets hospital level security and back-up requirements.

Privacy and data integrity between the user’s browser and the server is provided by mandatory use of Transport Layer Security (TLS), and a server certificate issued by TERENA (Trans-European Research and Education Networking Association). All trial sites will have access to REDCap. Site access is controlled with IP restriction.

## Archiving of data

The investigator and sponsor specific essential documents will be retained for at least 25 years. At that moment, it will be judged whether it is necessary to retain them for a longer period, according to applicable regulatory or other requirements.

[Fill in]

## Access to data

The investigators and institutions involved in the trial will permit clinical trial-related monitoring, audits and regulatory inspections (including provision of direct access to source data and documents).

Login in REDCap is password controlled. Each user will receive a personal login name and password and will have a specific role which has predefined restrictions on what is allowed in REDCap. Furthermore, users will only be able to see data of subjects of their own site. Any activity in the software is traced and transparent via the audit trail.

# Safety

## Definitions

|  |
| --- |
| **Adverse Events and Adverse Reactions** |
| **Term** | **Definition** |
| **Adverse Event (AE)** | Any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment. |
| **Unexpected Adverse Event** | An adverse event of which the nature or severity is not consistent with the Reference Safety Information (RSI) of the product (i.e. the applicable information in the Investigator’s Brochure (IB) for an investigational medicinal product which is not authorised or in the Summary of Product Characteristics (SmPC) for an authorised investigational medicinal product). |
| **Adverse Reaction (AR)** | An untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject. The phrase “response to an investigational medicinal product” means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions. |
| **Serious Adverse Event (SAE)** | Any untoward medical occurrence that:* requires inpatient hospitalisation or prolongation of existing hospitalisation;
* results in persistent or significant disability/incapacity;
* results in a congenital anomaly or birth defect;
* is life-threatening; *or*
* results in death.

Other important medical events may also be considered serious if they jeopardise the subject or require an intervention to prevent one of the above consequences.NOTE: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. |
| **Suspected Unexpected Serious Adverse Reaction (SUSAR)** | A serious adverse reaction, the nature, severity or outcome of which is not consistent with the Reference Safety Information (RSI). |

|  |
| --- |
| **Attributions** |
| **Term** | **Definition** |
| **Not related** | An adverse event which is not related to the use of the drug. |
| **Unlikely related** | An adverse event for which an alternative explanation is more likely - e.g. concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely. |
| **Possibly related** | An adverse event which might be due to the use of the drug. An alternative explanation - e.g. concomitant drug(s) or concomitant disease(s) - is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded. |
| **Probably related** | An adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely - e.g. concomitant drug(s) or concomitant disease(s). |
| **Definitely related** | An adverse event which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation - e.g. concomitant drug(s) or concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge). |

An adverse event is considered associated with the use of the drug if the attribution is ‘possibly’, ‘probably’ or ‘definitely related’.

## Reporting requirements

### AE reporting

All relevant AEs per subject will be recorded [Choose from list].

Special attention will be given to those subjects who have discontinued the trial for an AE, or who experienced a severe or a serious AE. These AEs should be recorded in the patient’s file and in the CRF.

### SAE reporting

SAEs occurring within a period of [Fill in] [Choose from list] following the last intake of study medication will be reported as below.

All serious adverse events (initial and follow up information – except for those, described in section 14.5) and events, described in section 14.2.4, occurring during this trial must be reported by the local PI within 24 hours after becoming aware of the event to:

* HIRUZ CTU of Ghent University Hospital;
* the CI;
* the company that provides the IMP (as stipulated in the agreement).

This reporting is done by using the appropriate SAE form. For the contact details, see below.

### SUSAR reporting

In case the Coordinating Investigator/sponsor, in consultation with HIRUZ CTU, decides the SAE is a SUSAR, HIRUZ CTU will report the SUSAR to the EMA, through the Eudravigilance (EV) database within the timelines as defined in European legislation. In case of a fatal or life-threatening SUSAR, the sponsor should report at least the minimum information as soon as possible and in any case no later than 7 calendar days after being made aware of the case. In case of a non life-threatening SUSAR the reporting process must be completed within 15 calendar days.

The Coordinating Investigator reports the SUSAR to all local PIs.

### Other reporting requirements

[Fill in]

## List of contact details for safety reporting

|  |  |  |
| --- | --- | --- |
| HIRUZ CTU | E | [hiruz.ctu@uzgent.be](https://infoland.ai.internal.uzgent.be/iProva/management/hyperlinkloader.aspx?hyperlinkid=e2132bab-403c-44fb-8b57-96537d07926a) |
| T | +32 9 332 05 00 |
| Coordinating Investigator (CI) | N | [Name CI] |
| E | [Fill in E-mail address] |
| T | [Fill in Telephone number] |
| Marketing Authorisation Holder (MAH) | N | [Fill in Company Name] |
| E | [Fill in E-mail address] |
| T | [Fill in Telephone number] |

## Flowchart reporting

|  |  |
| --- | --- |
| **Type of Adverse Event** | **Action(s) be taken** |
| **AE** | List all relevant AEs per subject in the patient’s file and add this information to the CRF. |
| **SAE** | * Notify to HIRUZ CTU and CI within 24 hours after becoming aware of the SAE;
* Add the SAE to a list that will be reported yearly (see section 14.7);
* Add the SAE in the CRF (please take into account section 14.5).
 |
| **SUSAR** | * Notify to HIRUZ CTU and CI within 24 hours after becoming aware of the SUSAR;
* HIRUZ CTU submits the SUSAR to the EMA (through EV database) after communication with the CI;
* Study team of CI informs company that provides the IMP (as stipulated in the agreement).
 |

Reporting to the local ethics committee of SAEs and SUSARs remains the responsibility of the PI and should be done in accordance with the requirements of the local institution’s procedure.

## Events excluded from reporting

[Fill in]

## Data Safety Monitoring Board (DSMB)

All trial medication is authorised and used in current practice. Considering the known safety profile of the trial medications and trial design, a DSMB is not foreseen.

## Annual Safety Report (ASR)

The Coordinating Investigator will provide an ASR once a year throughout the entire duration of this clinical trial, or on request, to the EMA. This ASR will include all SAEs and relevant safety information regarding all investigational medicinal products, used in this trial.

The report will be submitted no later than 60 calendar days after the ASR Data Lock Point (DLP). The first DLP is 1 year after the first date of the sponsor’s authorisation to conduct the clinical trial. Subsequently, the ASR will be submitted each year (+ maximum 60 days) until the trial is declared ended.

## Follow-up after an adverse reaction

[Fill in]

# Monitoring, audits and inspections

## Monitoring

### General

Monitoring of the trial will be performed in compliance with GCP E6(R2) and the applicable regulatory requirements. The study team will be trained during an initiation visit by the monitor. A detailed description of the monitoring tasks can be found in the latest version of the (study-specific) ‘Clinical Trial Monitoring Plan’.

### Monitoring team

Monitoring services will be provided by HIRUZ CTU. All relevant contact details (e.g. primary contact person) can be found in the ‘Clinical Trial Monitoring Plan’.

### Scope

Monitoring services will consist of the following (non-exhaustive list):

* review of informed consents and the followed process;
* check on recruitment status;
* checking for protocol deviations/violations;
* checking GCP compatibility;
* check on safety reporting compliance;
* IMP handling and storage;
* review of study data.

More information can be found in the Clinical Trial Monitoring Plan.

## Inspection

This trial can be inspected at any time by regulatory agencies during or after completion of the trial. Therefore access to all study records, including source documents, must be accessible to the inspection representatives. Subject privacy must be respected at all times, in accordance to GDPR, GCP and all other applicable local regulations.

The investigator/study team should immediately notify the sponsor if (s)he has been contacted by a regulatory agency concerning an upcoming inspection.

## Deviation policy

Sponsor and all investigators agree to take any reasonable actions to correct protocol or other deviations/violations noted during monitoring/inspection, in consultation with the monitoring team. All deviations must be documented on the correct deviation log by the study team that is kept available at any time for monitoring/inspection purposes. Under emergency circumstances, deviations from the protocol to protect the rights, safety or well-being of human subjects may take place without prior approval of the sponsor and the CA/IEC.

## Serious breach to GCP and/or the protocol

Critical issues that significantly affect patient safety, data integrity and/or study conduct should be clearly documented on the applicable deviation log and will be communicated with the Coordinating Investigator, HIRUZ CTU and possibly the CA/IEC.

Please contact HIRUZ CTU immediately in case of a serious breach: [hiruz.ctu@uzgent.be](https://infoland.ai.internal.uzgent.be/iProva/management/hyperlinkloader.aspx?hyperlinkid=7f3e8c83-587e-4934-9b70-a4ef28feba6d) and/or +3293320500.

Early termination of the trial (in a specific center or overall) may be necessary in case of major non-compliance.

# Ethical and legal aspects

## Good Clinical Practice

The trial will be conducted in accordance with the latest version of the ICH E6 (R2) GCP guidelines, creating a standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical studies that provides assurance that the data and reported results are accurate and that the rights, integrity and confidentiality of study subjects are protected.

## Informed consent

Eligible subjects may only be included in the trial after providing written (witnessed, if needed) IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the subject. Informed consent must be obtained before conducting any study-specific procedures (as described in this protocol).

Prior to entry in the trial, the investigator must explain the trial and the implication(s) of participation to potential subjects and/or their legal representatives. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. Participating subjects will be told that their records may be accessed by competent authorities and by authorised persons without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF), the subjects or legally acceptable representatives are authorising such access.

After this explanation and before entry to the trial, written, dated and signed informed consent should be obtained from the subject or legally acceptable representative. The ICF should be provided in a language sufficiently understood by the subject. Subjects must be given the opportunity to ask questions.

The subject or legally acceptable representative will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry to the trial, consent should be appropriately recorded by means of either the subject’s or his/her legal representative’s dated signature or the signature of an independent witness who certifies the subject’s consent in writing. After having obtained the consent, a copy of the ICF must be given to the subject.

In case the subject or legally acceptable representative is unable to read, an impartial witness must attest the informed consent.

Subjects who are unable to comprehend the information provided or pediatric subjects can only be enrolled after consent of a legally acceptable representative.

The following information should be added to the electronic patient dossier (EPD):

* which version of the ICF was obtained;
* who signed the ICF;
* if sufficient time has been given to consider participation into the trial;
* which investigator obtained ICF with the date of signature;
* if a copy was provided to the patient;
* start and end of participation in the trial.

## Approval of the study protocol

### General

The protocol has been reviewed and approved by the CA/IEC. This trial cannot start before their approval has been obtained, a trial initiation visit has been performed by the monitor and, if applicable, all necessary agreements are finalized.

### Protocol modifications and urgent safety measures

Any substantial change or addition to the protocol can only be made in a written protocol modification that must be approved by the CA/IEC.

Only modifications that are intended to eliminate an apparent immediate safety threat to the participants may be implemented immediately.

Notwithstanding the need for approval of formal protocol modifications, the investigators are expected to take any immediate action, required for the safety of any subject included in this trial, even if this action represents a deviation from the protocol. These actions should always be notified to the sponsor without undue delay, in order for the sponsor to notify the CA/IEC.

## Confidentiality and data protection

All study data will be handled in accordance with the law on General Data Protection Regulation (GDPR) and institutional rules (i.e. in accordance with the Belgian laws dated on 30-JUL-2018 and 22-AUG-2002).

The collection and processing of personal data from subjects enrolled in this trial will be limited to those data that are necessary to fulfill the objectives of the trial. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

Appropriate technical and organisational measures to protect the personal data against unauthorised disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor and site personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential. In case of data security breach, local institution’s procedures will be followed.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for trial-related monitoring, audit, Ethics Committee review and regulatory inspection. This consent also addresses the transfer of the data to other entities, if applicable.

Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

Stored samples will be [Choose from the list] throughout the sample storage and analysis process and will not be labeled with personal identifiers.

## Liability and insurance

This study protocol is without prejudice to national and European Union law on the civil and criminal liability of the Sponsor, Coordinating Investigator, Principal Investigator(s) and other parties concerned.

The sponsor has entered into a no-fault insurance policy for this trial, in accordance with the relevant legislation (article 12 of the Belgian Law of 7 May 2017 and article 76 of the EU Regulation 536/2014).

# Publication policy

[Fill in]

This trial will be registered at EU Clinical Trials (through CTIS), and results information from this trial will be submitted to aforementioned website. In addition, every attempt will be made to publish results in peer-reviewed journals.

# List of abbreviations

**Abbreviation.…………………………………………………………………………………….Page**

 AE = Adverse Event 18, 33, 34, 35

AR = Adverse Reaction 33

ASR = Annual Safety Report 36

AxMP = Auxiliary Medicinal Product 23, 24

CA = Competent Authority 4, 16, 17, 38, 40

CI = Coordinating Investigator 26, 31, 34, 35

CRF = Case Report Form 31, 34

CTIS = Clinical Trials Information System 42

CTR = Clinical Trial Regulation 2, 3

CTU = Clinical Trial Unit 34, 35, 37, 38

DLP = Data Lock Point 36

DSMB = Data Safety Monitoring Board 36

eCRF = electronic Case Report Form 19, 26, 31

EDC = Electronic Data Capture 31

EMA = European Medicines Agency 34, 36

EPD = Electronic Patient Dossier 39

EU = European Union 1, 9, 10, 11

EV = Eudravigilance 35

FVFS = First Visit First Subject 16

GCP = Good Clinical Practice 2, 3, 26, 37, 38, 39

GDPR = General Data Protection Regulation 37, 40

HIRUZ = Health, Innovation and Research Institute 31, 34, 35, 37, 38

IB = Investigator’s Brochure 33

ICF = Informed Consent Form 39

ICH = International Conference on Harmonisation 26, 39

IEC = Independent Ethics Committee 4, 16, 17, 38, 39, 40

IMP = Investigational Medicinal Product 21, 22, 34, 37

IP = Internet Protocol 31

MAH = Marketing Authorisation Holder 35

PI = Principal Investigator 19, 26, 27, 34, 35

RAP = Risk Assessment Plan 13

REDCap = Research Electronic Data Capture 31, 32

RSI = Reference Safety Information 33

SAE = Serious Adverse Event 33, 34, 35, 36

SmPC = Summary of Product Characteristics 33

SUSAR = Suspected Unexpected Serious Adverse Reaction 33, 34, 35

TERENA = Trans-European Research and Education Networking Association 31

TLS = Transport Layer Security 31

# List of references

[Fill in]

# Appendices

## Appendix 1: [Fill in]

[Add Appendix]

## Appendix 2: [Fill in]

[Add Appendix]